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Palladium-Catalyzed Amination of Aryl Sulfides with Aliphatic Amines

Ke Gao,[a] Hideki Yorimitsu,*[a,b] and Atsuhiro Osuka[a]

Abstract: Conditions for palladium-NHC-catalyzed amination of aryl sulfides have been improved to allow for the use of aliphatic amines as well as aromatic amines and to exhibit wider functional group tolerance. The KHMDS-mediated amination of heteroaryl sulfides could proceed without palladium. Based on distinct difference in reactivities of C–Br and C–S bonds, sequential amination of bromothioanisole proceeds to install two different alkylamino groups onto the aromatic ring in one pot.

Introduction

The prevalence of aniline derivatives in pharmaceutical, agrochemical, and material sciences has been inspiring organic chemists to develop efficient methods for carbon–nitrogen bond formation.[1] After Buchwald's and Hartwig's breakthrough on palladium-catalyzed amination of aryl halides with anilines, a number of catalytic amination reactions of aryl halides/pseudohalides have been reported.[2,3] Recently, a series of stable and low cost phenol derivatives[4] such as carbamates,[5] sulfamates,[5b,6] pivalate esters,[7] phosphates[8] and even challenging methyl ethers[9] have been introduced as substrates of amination reactions. This situation encouraged us to discover new coupling partners for amination reactions other than oxygen-based molecules.

Although a carbon–sulfur bond has reactivity comparable to carbon–halogen bonds, it has been used much less frequently in transition metal-catalyzed cross-coupling reactions due to the strong affinity of sulfur atom to transition metals.[10] Therefore, development of new catalytic transformations of C–S bonds would be an important challenge since C–S bonds exist widely in organic feedstock, synthetic intermediates, and useful products. As a part of our recent contribution to catalytic C–S bond cleavage,[11] we reported the first palladium-catalyzed amination of aryl sulfides (Scheme 1).[11c] A palladium–NHC (*N*-heterocyclic carbene) precatalyst SingaCycle-A3 exhibited excellent reactivity on C–S bond cleavage. However, there still remain some drawbacks: (1) the amine nucleophile is limited to aniline derivatives and (2) carbonyl functionalities are incompatible with highly basic conditions (excess $KN(SiMe_3)_2$, 100 °C). Here, we report a milder and more general protocol for catalytic amination of aryl sulfides.

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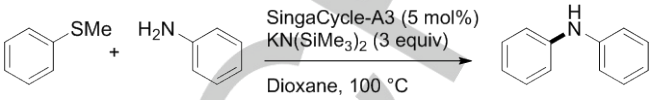
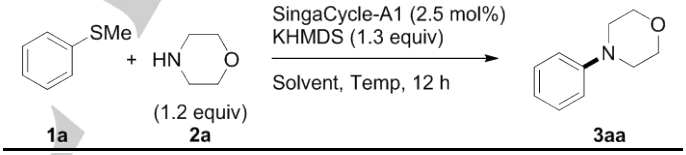


Scheme 1. Previous palladium-catalyzed amination of aryl sulfides with anilines.

Results and Discussion

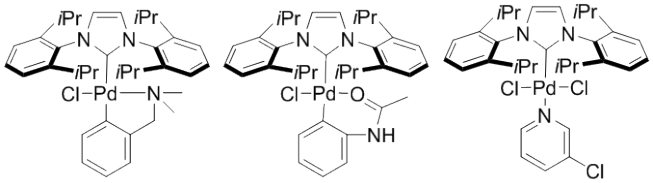
To optimize conditions, we chose thioanisole (**1a**) and morpholine (**2a**) as model substrates. Since NHC ligands are uniquely effective for the previous amination *via* C–S bond cleavage, modification of NHC ligands was our first strategy to achieve the amination. Thus, a variety of NHC ligands were synthesized to screen reaction conditions. However, any modified NHC ligands other than IPr•HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) were less effective

Table 1. Optimization of conditions[a]



1a **2a** **3aa**

Entry	Catalyst	Temp (°C)	Solvent	Yield (%)[b]
1	SingaCycle-A3	100	Dioxane	18
2	SingaCycle-A1	100	Dioxane	29
3	[IPrPdCl(π-allyl)]	100	Dioxane	17
4	Pd-PEPPSI-IPr	100	Dioxane	13
5	SingaCycle-A1	100	THF	52
6	SingaCycle-A1	100	Hexane	73
7	SingaCycle-A1	100	Toluene	98[c]
8	SingaCycle-A1	60	Toluene	99[c]



SingaCycle-A1 SingaCycle-A3 Pd-PEPPSI-IPr

[a] The reaction was performed on a 0.5 mmol scale. [b] Determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

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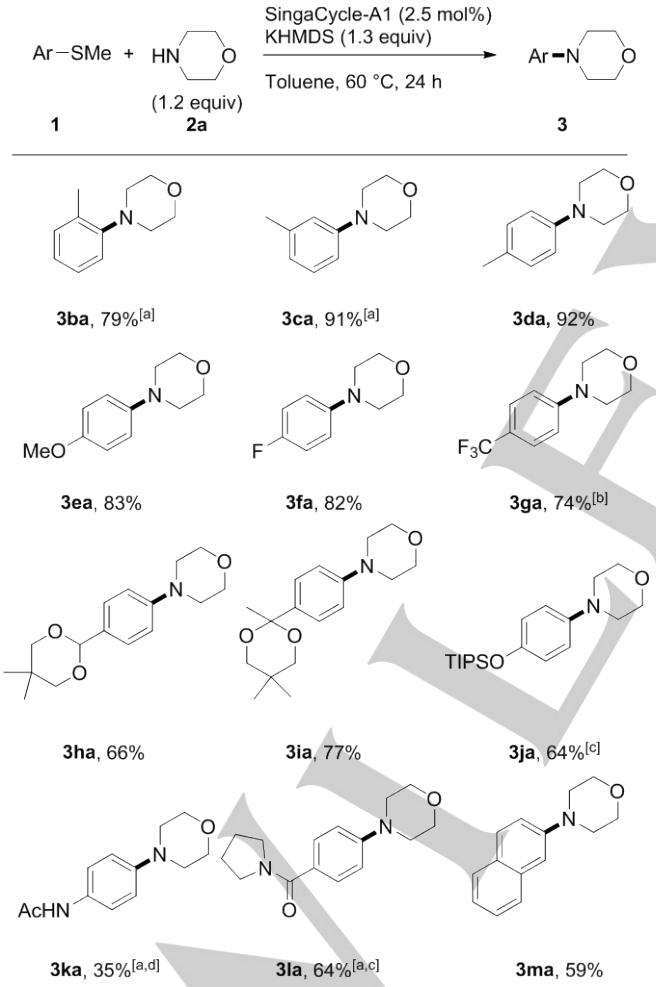
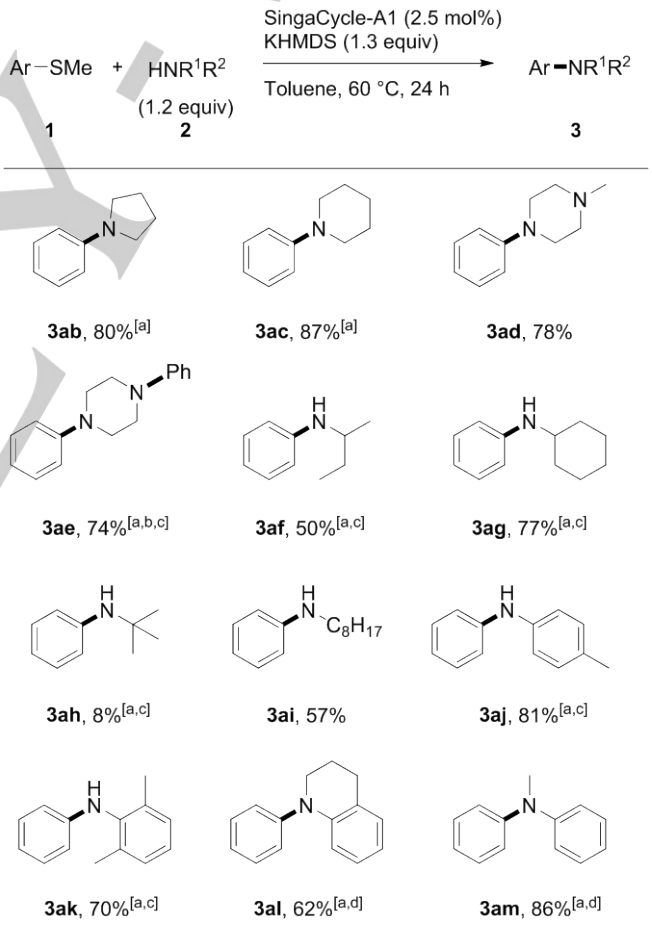
(Table S1).[12] Therefore, we then screened various Pd-IPr precatalysts for the amination reaction. The results are summarized in Table 1. SingaCycle-A3[13] in combination with $KN(SiMe_3)_2$ (KHMDS), which worked previously in the amination with anilines,[11c] afforded the corresponding amination product **3aa** in only 18% yield (entry 1). In the presence of SingaCycle-A1,[14] the yield of the desired product was increased to 29% (entry 2). Other palladium precatalysts such as [IPrPdCl(π-allyl)][15] and Pd-PEPPSI-IPr[16] were less effective (entries 3 and 4). The choice of the base, KHMDS, is critical for the reaction as other organic and inorganic bases including Grignard reagents, KO*t*Bu, and K_2CO_3 afforded trace amounts of **3aa** or were totally ineffective. Importantly, nonpolar solvents worked much better than polar solvents (entries 5-7). The reaction afforded **3aa** in 98% yield in toluene (entry 7). Furthermore, we are delighted to find that the reaction could take place even at 60 °C to afford **3aa** in 99% isolated yield (entry 8).

With the optimized conditions in hand, we examined the amination of various aryl sulfides with morpholine (Scheme 2). Sterically hindered *ortho*-methylphenyl sulfide **1b** afforded the desired product **3ba** in 79% yield at 80 °C. Both electron-donating and electron-withdrawing groups at the *para* position of aryl sulfides did not have significant effect on reaction efficiency (**3da**-**3la**). *para*-Trifluoromethylphenyl sulfide was aminated with morpholine to yield **3ga** while attempted amination with aniline failed in the previous report.[11c] The reaction showed reasonable compatibility with functional groups including protected aldehyde (**3ha**) and ketone (**3ia**), TIPS-protected phenol (**3ja**), acetanilide (**3ka**), and amide (**3la**).

Subsequently, we explored the amination reaction of aryl sulfide with various amines (Scheme 3). Cyclic amines including piperidine, pyrrolidine, and 1-methylpiperazine reacted smoothly with thioanisole to afford the corresponding amination products **3ab**-**3ad** in good yields. The reaction of piperazine afforded diarylation product **3ae** in good yield with 2.2 equiv of thioanisole.



Scheme 2. Palladium-catalyzed amination of aryl sulfides with morpholine. The reaction was performed on a 0.5 mmol scale. [a] The reaction was performed at 80 °C. [b] *p*-$CF_3C_6H_4SC_{12}H_{25}$ was used. [c] 5 mol% SingaCycle-A1, TIPS = triisopropylsilyl. [d] 10 mol% SingaCycle-A1 and 2.3 equiv of KHMDS were used.



Scheme 3. Palladium-catalyzed amination of aryl sulfides with various amines. The reaction was performed on a 0.5 mmol scale. [a] The reaction was performed at 80 °C. [b] 2.2 equiv of **1a** was used. Piperazine is the limiting substrate. [c] 5 mol% SingaCycle-A1. [d] 10 mol% SingaCycle-A1.

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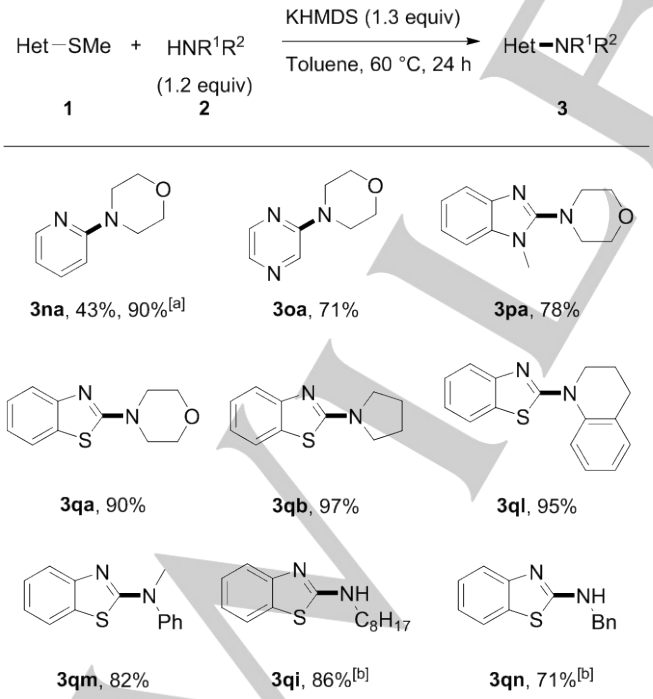
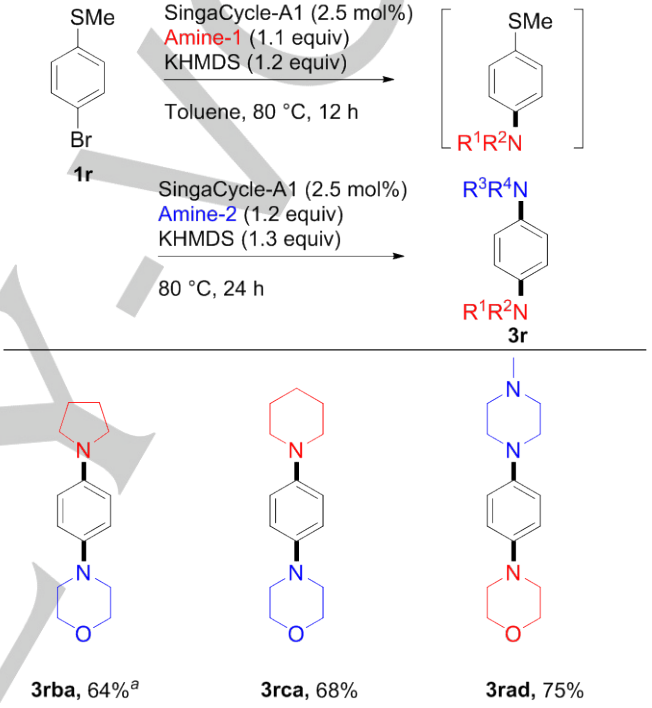
sec-Butylamine and cyclohexylamine also reacted in the presence of 5 mol% SingaCycle-A1 at 80 °C to afford secondary amines **3af** and **3ag** without formation of diphenylated tertiary amines. Bulky *tert*-butylamine afforded product **3ah** in miserable yield. The reaction of sterically less demanding octylamine afforded the desired product **3ai** in 57% yield along with a diarylation product in 11% yield. The present conditions are also applicable to the amination with aromatic *p*-toluidine to afford **3aj** in 81% yield at 80 °C, proving comparable to the previous conditions.[11c] Moreover, sterically hindered 2,6-dimethylaniline, 1,2,3,4-tetrahydroquinoline and *N*-methylaniline were involved in the amination to yield the corresponding products **3ak**, **3al** and **3am**, respectively, in good yields.

The amination of heteroaryl sulfides were also examined (Scheme 4). We are delighted to find that the reaction could proceed in the absence of SingaCycle-A1. The catalyst-free amination of 2-pyridyl sulfide afforded product **3na** in 43% yield, while the yield could increase to 90% in the presence of SingaCycle-A1. Other heteroaryl sulfides such as 2-pyrazyl sulfide, 2-(1-methylbenzimidazolyl), and 2-benzothiazolyl sulfide were aminated with morpholine smoothly to afford the corresponding products **3oa**, **3pa**, and **3qa**, respectively. Both primary and secondary amines reacted with 2-benzothiazolyl sulfide to afford the amination products **3qb**-**3qm** in good to excellent yields. Similar displacement of heteroaryl sulfones and sulfoxides with amines is known.[17,18] However, there are rare reports of direct displacement of heteroaryl sulfides with amines with limited examples.[19] The KHMDS-mediated amination of heteroaryl sulfides provides a more general protocol for the functionalization of heteroaryl sulfides.



Scheme 4. Catalyst-free amination of heteroaryl sulfides with various amines. The reaction was performed on a 0.5 mmol scale. [a] In the presence of SingaCycle-A1 (2.5 mol%). [b] 2.2 equiv of amine and 2.3 equiv of KHMDS were used.

We found that the amination reactions of *p*-bromothioanisole proceeded preferentially at the C-Br bond while the C–S bond remained untouched (Scheme 5). The exclusive conversions of the C–Br bond allowed us to install two different amino groups onto the aromatic ring in one pot. The second amination was highly selective to afford diaminobenzenes **3rba**, **3rca**, and **3rad** in high yields.



Scheme 5. The amination of heteroaryl sulfides with various amines. The reaction was performed on a 0.5 mmol scale. [a] 5 mol% SingaCycle-A1 was used in the second amination.

Conclusions

We have developed palladium-catalyzed amination of aryl sulfides with aliphatic amines. The reaction proceeded under milder conditions compared to the previous amination with aromatic amines. The amination of heteroaryl sulfides could proceed in the absence of a palladium catalyst. The different reactivities of a C–S bond and a C–Br bond allowed us to install different amino groups onto an aromatic ring in one pot, which could be a useful protocol for organic synthesis.

Experimental Section

General procedure for palladium-catalyzed amination of aryl sulfides with aliphatic amines

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In a Schlenk tube were placed SingaCycle-A1 (8.3 mg, 0.0125 mmol), thioanisole (**1a**, 62.1 mg, 0.50 mmol), and morpholine (**2a**, 52.3 mg, 0.60 mmol). To the mixture was added a toluene solution of $KN(SiMe_3)_2$ (0.5 M, 1.3 mL, 0.65 mmol). The resulting mixture was stirred at 60 °C for 12 h. The reaction was quenched by addition of saturated NH_4Cl solution (1.0 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1–5/1) to afford the desired product **3aa** as an orange solid (82.2 mg, 0.50 mmol, 99%).

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Keywords: Amination • Aryl sulfides • C–S bond cleavage • N-heterocyclic carbene ligands • Palladium

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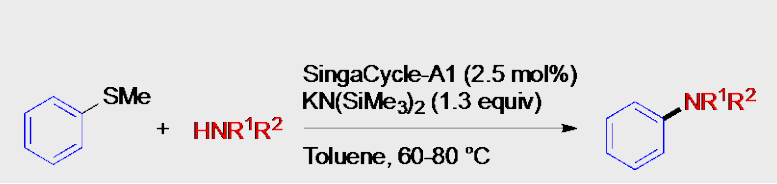

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A palladium-NHC precatalyst exhibits high efficiency on C–S bond cleavage for amination of aryl sulfides with aliphatic amines as well as aromatic amines.

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